## REMARKS

Claims 1, 9 and 18 have been amended herein. Please cancel claims 12-15 and 19-22 without disclaimer or prejudice. Claims 31-33 were previously cancelled without prejudice. Subsequent to the entry of the present amendment, claims 1-30 are pending and at issue. The amendment adds no new matter, as the claim language is fully supported by the specification and original claims.

### I. Rejection under 35 USC § 102

Claims 18-19, 22-24 and 27-28 stand rejected under 35 USC §102 as allegedly anticipated by US 5,587,363 (hereinafter, "Henderson"). Applicants respectfully traverse this rejection on the following grounds.

To anticipate a claim, the single prior art reference must disclose each and every element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir. 1990); *Connell v. Sears Roebuck & Co.*, 220 USPQ 193, 198 (Fed. Cir. 1983); MPEP §2131. There must be no difference between the reference disclosure and the claimed invention. *Scripps Clinic & Research Found. v. Genentech, Inc.*, 18 USPQ2d 1001 (Fed. Cir. 1991). Furthermore, the elements must be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990).

The Office Action alleges that "Henderson teaches the use of composition comprising glucosamine for the treatment of connective tissue and cartilage repair and arthritis/pain" and "dosages of the aminosugars for the said treatments." (Office Action, pages 4-5.)

Independent claim 18 recites "[a] method of treating a joint comprising the steps of: a. diagnosing a pathological marker associated with a joint condition; and b. administering an aminosugar in a therapeutically effective formulation." Without acquiescing to the reasoning offered by the Office Action, in order to expedite prosecution towards allowance, Applicants have amended claim 18 herein to read "[a] method of treating synovitis or subchondral bone edema comprising the steps of: a. diagnosing a pathological marker associated with synovitis or subchondral bone edema; and b. administering an aminosuger in a therapeutically effective formulation, wherein said aminosugar is selected from the group consisting of N-acetylglucosamine, glucosamine, galactosamine, N-acetylgalactosamine, iminocyclitol, and pharmaceutically acceptable salts thereof," thereby rendering the rejection moot.

Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. 102(b) be withdrawn.

## II. Rejection under 35 USC § 103

Claims 1-8, 10-11, 18-22, 24-25, 27-29 are rejected under 35 U.S.C. §103 as allegedly obvious over Weidner (WO 03/002117) in view of Speck, US 4,870,061 (hereinafter, "Speck"), and Nanba, US 5,169,636 (hereinafter, "Nanba"). This rejection is respectfully traversed on the following grounds.

The U.S. Supreme Court decision in the *KSR International v. Teleflex Inc.* (82 USPQ2d 1385), modified the standard for establishing a *prima facie* case of obviousness. Under the KSR rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references.

In addition, the U.S. Court of Appeals for the Federal Circuit interpreted *KSR v. Teleflex* (*Id.*) in pertinent part:

> In order to find a *prima facia* case of unpatentability ... a showing that the "prior art would have *suggested* making the specific molecular modifications necessary to achieve the claimed invention" was also required. *Id.* (citing *In re Jones*, 958 F.2d 347 (Fed. Cir.

1992); Dillon, 919 F.2d 688; Grabiak, 769 F.2d 729; *In re Lalu*, 747 F.2d 703 (Fed. Cir. 1984)) (*See Takeda v. Alphapharm*, 492 F.3d 1350, Fed. Cir. 2007).

Applicants respectfully submit that the Office Action has not established a *prima facie* case of obviousness.

The pending independent claims as currently amended are:

1. A method of treating a pathology in a mammal, said pathology being synovitis or subchondral bone edema, wherein said treatment comprises administering to said mammal a therapeutically effective amount of an aminosugar, wherein the aminosugar is injected intra-articularly.

9. A method of treating pathologies associated with synovitis or subchondral bone edema comprising administering a therapeutically effective amount of N-acetylglucosamine as a controlled release formulation.

18. A method of treating synovitis or subchondral bone edema comprising the steps of: a. diagnosing a pathological marker associated with synovitis or subchondral bone edema; and b. administering an aminosuger in a therapeutically effective formulation, wherein said aminosugar is selected from the group consisting of N-acetylglucosamine, glucosamine, galactosamine, N-acetylgalactosamine, iminocyclitol, and pharmaceutically acceptable salts thereof.

*Pending claims are not obvious over Weidner*

The Office Action alleges, in pertinent part, that Weidner teaches the treatment of osteoarthritis and synovitis via administration of aminosugar comprising compositions comprising effective amounts of the aminosugar(s) to individuals suffering from osteoarthritis/ degenerative arthritis. (Office Action, page 5). However, a review of Weidner reveals that the cited reference **teaches away** from the present invention. In particular, Weinder states that the use of aminosugars or glycosaminoglycans has resulted in **some** relief of symptoms. (Page 2, lines 21-22.) Weidner recites the need for a "combination of niacinamide and an aminosugar" having immunomodulating activities and significantly suppressing inflammatory reactions and hypersensitivity in mammals. (Page 3, Lines 33-34). The combination is provided in the form

of a "**chemical complex consisting of one or more optionally substituted pyridine carboxy derivative(s) or salt(s) thereof and one or more optionally substituted aminosugar(s) or salt(s) thereof.**" (Page 3, Lines 35-38).

The invention by Weidner is repeatedly defined as a "composition" or a "chemical complex" which indicates more than a single ingredient. Applicant respectfully disagrees that "Weidner's teaching indicates that cartilage degredation and synovitis can be treated via administration of aminosugars via injection." (Office Action page 6). Weidner's invention comprises the administration of "an effective amount of a combination of one or more optionally substituted pyridine carboxy derivative(s) or salt(s) thereof and one or more optionally substituted aminosugar(s) or salt(s) thereof, or a chemical complex comprising said combination." (Page 19, Lines 33-36). Therefore, one of ordinary skill in the art would not practice Applicants' invention using the teachings of the cited reference, because one of ordinary skill in the art would not use an aminosugar alone as claimed in the present invention.

The cited reference also teaches away from utilizing aminosugars consisting of more than 6 saccharide units. The compositions according to the invention **do not** comprise both a glucosamine or a chondroitin. (Page 14, Lines 10-12).

Weidner also teaches administration of **said combination of said chemical complex** via injection. However, in a most preferred embodiment of the invention the compositions or complexes are used for topical administration. (Page 14, Line 32-34). Again, "preferable manners of administration are oral and/ or topical. (Page 22, Line 3). In addition, Weidner does not teach the method of administering a therapeutically effective amount of an aminosugar by injection. One of ordinary skill in the art would not administer an aminosugar intra-articularly in view of Weidner.

Therefore, the reference teaches away from the present invention, since the impression left to the skilled artisan is that the ultimate result of practicing the claimed method would not have the property sought by the Applicants. *In re Caldwell*, 319 F.2d 254, 256, 138 USPQ 543 (CCPA 1963).

Furthermore, there is nothing in Weidner which discloses or suggests the method of treating synovitis or subchondral bone edema comprising the steps of: a) diagnosing a pathological marker associated with synovitis or subchondral bone edema; and b) administering

an aminosugar in a therapeutically effective formulation wherein said aminosugar is selected from the group consisting of N-acetylglucosamine, glucosamine, galactosamine, N-acetylgalactosamine, iminocyclitol, and pharmaceutically acceptable salts thereof. Applicants submit that because diagnosing a pathological marker associated with a joint condition is clearly necessary as a requisite property of the ultimate product of the method steps, the method of treating a joint condition as claimed in Claim 18 becomes an impossibility.

Therefore, there is no suggestion or motivation to modify Weidner to arrive at the invention as claimed with a reasonable expectation of success. Furthermore, the cited reference does not teach or suggest all of the recited claim limitations. As such, no *prima facie* case for obviousness exists.

*Pending claims are not obvious over Speck*

The Examiner agrees that Speck does not exemplify such a method for treatment of cartilage degradation, synovitis, and subchondral bone edema, via administration of active agents other than N-acetylglucosamine, the various forms of administration, combination therapy of aminosugars with anti-inflammatory drugs and hexoaminidase inhibitors. (Office Action, page 6). However, the Office Action maintains that Speck teaches a mode of administration that is the same mode of administration used in the methods of treatment as instantly claimed. (Office Action, page 6). There are only a limited number of ways to introduce a substance or therapy into the body. Even though the same ways can be used the substance or therapy does not necessarily the same. In order to be thorough the cited reference discusses all the possible ways to introduce N-acetylglucosamine into the body. Recitation of these ways does not amount to an obvious method of achieving the successful results in the present application.

Applicant holds that Speck **teaches away** from the present invention of using intra-articular injection. In particular, Speck states that injection of glucosamine is undesirable because an injection preparation is unstable in solution and as such has to be prepared, stored and delivered with an acidic pH-value and has to be neutralized by a physician before use, and a local anesthetic, such as lidocaine, which can cause adverse side effects, has to be used. (Column 2, lines 15-35.) Speck recites that buccal administration of N-acetylglucosamine solves the problem associated with administration via injection. (Column 3, lines 5-7.) Therefore, one of

ordinary skill in the art would not practice Applicants' invention using the teachings of the cited reference, because one of ordinary skill in the art would not administer an aminosugar by intra-articular injection in view of Speck.

Therefore, the reference teaches away from the present invention, since the impression left to the skilled artisan is that the ultimate result of practicing the method would not have the property sought by the Applicants. *In re Caldwell*, 319 F.2d 254, 256, 138 USPQ 543 (CCPA 1963).

Furthermore, there is nothing in Speck which discloses or suggests the method of treating synovitis or subchondral bone edema comprising the steps of: a) diagnosing a pathological marker associated with synovitis or subchondral bone edema; and b) administering an aminosugar in a therapeutically effective formulation wherein said aminosugar is selected from the group consisting of N-acetylglucosamine, glucosamine, galactosamine, N-acetylgalactosamine, iminocyclitol, and pharmaceutically acceptable salts thereof. Applicants submit that because diagnosing a pathological marker associated with a joint condition is clearly necessary as a requisite property of the ultimate product of the method steps, the method of treating a joint condition as claimed in Claim 18 becomes an impossibility.

Therefore, there is no suggestion or motivation to modify Speck to arrive at the invention as claimed with a reasonable expectation of success. Furthermore, the cited reference does not teach or suggest all of the recited claim limitations. As such, no *prima facie* case for obviousness exists.

*Pending claims are not obvious over Nanba*

The Office Action alleges that Nanba et al. teach compositions comprising oligosaccharides comprising glucosamine and galactosamine residues entrapped by liposomes and that liposomes are models for biological membranes and are effective in stabilizing drugs and achieving sustained release of drugs in vivo. (Office Action, pages 7-8) This is incorrect. Nanba recites liposomes which are made up of a liposome lipid membrane containing a glycolipid. (Column 1, lines 66 to column 2, line 16) A glycolipid is a lipid attached to a carbohydrate. A glycolipid is not an aminosugar. An **amino sugar** contains an amine group in place of a hydroxyl. A glycolipid's role is to provide energy and is a marker for cellular

recognition. The purpose of the liposome is to transport a target drug to an area without being recognized by the body as an antigen. The cellular recognition allows liposomes to remain in the body for a longer period of time increasing the likelihood of the drug reaching the target area. The glucosamine used by Applicants **is** the drug. The glucosamine used by Nanba is used to formulate the liposome. Nanba does not disclose or suggest a method of treating a pathology in a mammal by administering a therapeutically effective amount of an aminosugar, wherein the aminosugar is injected intra-articularly.

Neither does Nanba disclose or suggest the method of treating synovitis or subchondral bone edema comprising the steps of: a) diagnosing a pathological marker associated with synovitis or subchondral bone edema; and b) administering an aminosugar in a therapeutically effective formulation wherein said aminosugar is selected from the group consisting of N-acetylglucosamine, glucosamine, galactosamine, N-acetylgalactosamine, iminocyclitol, and pharmaceutically acceptable salts thereof.Applicants submit that because diagnosing a pathological marker associated with a joint condition is clearly necessary as a requisite property of the ultimate product of the method steps, the method of treating a joint condition as claimed in Claim 18 becomes an impossibility.

Therefore, there is no suggestion or motivation to modify Nanba to arrive at the invention as claimed with a reasonable expectation of success. Furthermore, the cited reference does not teach or suggest all of the recited claim limitations. As such, no *prima facie* case for obviousness exists.

## III. Rejection under 35 USC § 103

Claims 4, 7-8, and 30 are rejected under 35 U.S.C. §103(a) as allegedly obvious over Weidner (WO 03/002117) in view of Speck, US 4,870,061 (hereinafter, "Speck"), and Burger, US 5,843,919 (hereinafter, "Burger"). This rejection is respectfully traversed on the following grounds.

Weidner and Speck have been discussed above. The Examiner agrees that neither Weidner nor Speck teach a method of treatment that uses the formulations as instantly claimed in the form of an implant, gel and a combination therapy which includes anti-inflammatory drugs. (Office Action, page 8).

*Pending claims are not obvious over Burger*

The Office Action alleges that Burger teaches the treatment of arthritis/osteoarthritis using compositions comprising a combination of glucosamine and N-acetyl glucosamine. (Office Action, page 8.) However, a review of Burger reveals that the cited reference **teaches away** from the present invention.

The Office Action states, "According to Burger medications for the treatment of osteoarthritis include anti-inflammatory compounds. This means that anti-inflammatory compounds can be combined with aminosugars for the treatment of cartilage degradation." (Office Action, page 8). This in an inference by the Examiner. There is no **actual** reference in Burger that describes the use of anti-inflammatory drugs in conjunction or combination with aminosugars. In particular, Burger states, "Presently available medications for the treatment of osteoarthritis include anti-inflammatory compounds..." (Col. 1, Lines 31-33). Burger continues, "Little if any success has been reported in treatment of osteoarthritis, however, with glucosamine or omega-3 fatty- acids." (Col. 1, Lines 52-54). According to Burger, "omega-3-fatty acids have been suggested to have anti-inflammatory properties." (Col.1, Lines 47-48). Therefore, one of ordinary skill in the art would not practice Applicants' invention using the teachings of the cited reference, because one of ordinary skill in the art would not use an aminosugar alone as claimed in the present invention.

Therefore, the reference teaches away from the present invention, since the impression left to the skilled artisan is that the ultimate result of practicing the claimed method would not have the property sought by the Applicants. *In re Caldwell*, 319 F.2d 254, 256, 138 USPQ 543 (CCPA 1963).

Furthermore, there is nothing in Burger which discloses or suggests the method of treating synovitis or subchondral bone edema comprising the steps of: a) diagnosing a pathological marker associated with synovitis or subchondral bone edema; and b) administering an aminosugar in a therapeutically effective formulation wherein said aminosugar is selected from the group consisting of N-acetylglucosamine, glucosamine, galactosamine, N-acetylgalactosamine, iminocyclitol, and pharmaceutically acceptable salts thereof.Applicants submit that because diagnosing a pathological marker associated with a joint condition is clearly

necessary as a requisite property of the ultimate product of the method steps, the method of treating a joint condition as claimed in Claim 18 becomes an impossibility.

Therefore, there is no suggestion or motivation to modify Burger to arrive at the invention as claimed with a reasonable expectation of success. Furthermore, the cited reference does not teach or suggest all of the recited claim limitations. As such, no *prima facie* case for obviousness exists.

## IV. Rejection under 35 USC § 103

Claims 3-4, 6-8, are rejected under 35 U.S.C. §103(a) as allegedly obvious over Weidner (WO 03/002117) in view of Speck, US 4,870,061 (hereinafter, "Speck"), and Woerly, US 5,863,551 (hereinafter, "Woerly"). This rejection is respectfully traversed on the following grounds.

Weidner and Speck have been discussed above. The Examiner agrees that, both do not teach a method of treatment that uses the formulation as instantly claimed in the form wherein the aminosugar is entrapped in a matrix, a hydrogel and other forms of gels. (Office Action, page 10).

*Pending claims are not obvious over Woerly*

The Office Action alleges in pertinent part that Woerly teaches polymer hydrogels as implants for tissue replacement and regeneration, and that one of skill in the art would recognize the use of the hydrogels for the treatment of degenerative diseases. (Office Action, page 10). Woerly shows that the polymer hydrogels are used to replace or restore missing cells or organs. In one aspect of the invention, Woerly describes the structure of a matrix including complex sugars, "the polymer matrices may be formed…of an effective amount of the following components." (col.8, lines 17-21). However, Woerly does not describe using the sugars as the "medicinal part" of a treatment. The N-acetyl glucosamine in Woelry is a component of the structure not the targeted therapeutic element. Nothing in the cited reference discloses nor suggests a method of treating a pathology in a mammal by administering a therapeutically effective amount of an aminosugar, wherein the aminosugar is injected intra-articularly.

Neither does Woerly disclose or suggest the method of treating synovitis or subchondral bone edema comprising the steps of: a) diagnosing a pathological marker associated with synovitis or subchondral bone edema; and b) administering an aminosugar in a therapeutically effective formulation wherein said aminosugar is selected from the group consisting of N-acetylglucosamine, glucosamine, galactosamine, N-acetylgalactosamine, iminocyclitol, and pharmaceutically acceptable salts thereof.Applicants submit that because diagnosing a pathological marker associated with a joint condition is clearly necessary as a requisite property of the ultimate product of the method steps, the method of treating a joint condition as claimed in Claim 18 becomes an impossibility.

Therefore, there is no suggestion or motivation to modify Woerly to arrive at the invention as claimed with a reasonable expectation of success. Furthermore, the cited reference does not teach or suggest all of the recited claim limitations. As such, no *prima facie* case for obviousness exists.

## V. Rejection under 35 USC § 103

Claim 30 is rejected under 35 U.S.C. §103(a) as allegedly obvious over Weidner (WO 03/002117) in view of Speck, US 4,870,061 (hereinafter, "Speck"), and Wong et al., WO 00/68194 (hereinafter, "Wong"). This rejection is respectfully traversed on the following grounds.

Weidner and Speck have been discussed above. The Examiner agrees that neither Weidner nor Speck teach a method of treatment that uses the formulation that has the aminosugar in combination with hexoaminidase inhibitors.

*Pending claims are not obvious over Wong*

The Office Action alleges that Wong et al. teach that hexoaminidases catalyze cartilage erosion in arthritic subjects from over catabolism of glycosaminoglycans that fill the cartilage tissue and that it would have been obvious to one of ordinary skill in the art to make a formulation comprising amino sugars and use it in a method of treatment as claimed. (Office Action, page 9.) As set forth above, Weidner, Speck, and Burger **teach away** from the use of glucosamine alone to treat cartilage degradation.

The Office Action states, "This means iminocyclitols can be used in combination with glucosamine and galactosamine and their salts, N-acetyl derivatives for the treatment of cartilage degradation. (Office Action, pages 11 -12). The Examiner fails to cite where Wong possessed the concept of using iminocyclitols in combination with glucosamine and galactosamine and their salts. This is an inference. This may seem obvious to the Examiner now but Wong does not teach this combination. One of ordinary skill in the art would not use a therapeutically effective amount of an aminosugar, wherein the aminosugar is injected intra-articularly in a method of treatment as presently claimed.

Nor does Wong disclose or suggest the method of treating synovitis or subchondral bone edema comprising the steps of: a) diagnosing a pathological marker associated with synovitis or subchondral bone edema; and b) administering an aminosugar in a therapeutically effective formulation wherein said aminosugar is selected from the group consisting of N-acetylglucosamine, glucosamine, galactosamine, N-acetylgalactosamine, iminocyclitol, and pharmaceutically acceptable salts thereof.. Applicants submit that because diagnosing a pathological marker associated with a joint condition is clearly necessary as a requisite property of the ultimate product of the method steps, the method of treating a joint condition as claimed in Claim 18 becomes an impossibility.

Therefore, there is no suggestion or motivation to modify Wong to arrive at the invention as claimed with a reasonable expectation of success. Furthermore, the cited reference does not teach or suggest all of the recited claim limitations. As such, no *prima facie* case for obviousness exists.

## VI. Rejection under 35 USC § 103

Claims 1,2, 4-5, 7-9, 12, 14, 19, 21 and 29-30 are rejected under 35 U.S.C. §103(a) as allegedly obvious over Weidner (WO 03/002117) in view of Speck, US 4,870,061 (hereinafter, "Speck"), and Petrus et al., US 6,656,925 (hereinafter, "Petrus"). This rejection is respectfully traversed on the following grounds.

Weidner and Speck have been discussed above. The Examiner agrees that both Weidner and Speck do not teach a method of treatment of subchondral bone edema using amniosugars in the form of a controlled release formulation.

*Pending claims are not obvious over Petrus*

The Office Action alleges that Petrus et al. teach that during the inflammatory process vasoactive substances are released at the site of inflammation and cause edema. (col. 1, line 36-through col. 2, line 8). After careful review, Petrus states that the use of an aminosugar alone is ineffective as a therapeutic composition. (col. 10, lines 55-59). Examples 1 through 4 show that treatment with **both** glucosamine sulfate and zinc acetate was needed to treat osteoarthritis. (col. line 50 through col. 10, line 53). The cited reference **teaches away** from the results Applicant has shown. One of ordinary skill in the art would not use a therapeutically effective amount of an aminosugar, wherein the aminosugar is injected intra-articularly in a method of treatment as presently claimed.

Nor does Petrus disclose or suggest the method of treating synovitis or subchondral bone edema comprising the steps of: a) diagnosing a pathological marker associated with synovitis or subchondral bone edema; and b) administering an aminosugar in a therapeutically effective formulation wherein said aminosugar is selected from the group consisting of N-acetylglucosamine, glucosamine, galactosamine, N-acetylgalactosamine, iminocyclitol, and pharmaceutically acceptable salts thereof. Applicants submit that because diagnosing a pathological marker associated with a joint condition is clearly necessary as a requisite property of the ultimate product of the method steps, the method of treating a joint condition as claimed in Claim 18 becomes an impossibility.

In summary, the cited references do not render Applicants claimed method obvious. None of these references, either alone or in combination, teach or suggest Applicants invention.

The Examiner bears the burden of establishing a *prima facie* case of obviousness. *In re Oetiker*, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). In doing so, the Examiner must determine whether or not the prior art provides the "teaching or suggestion to one of ordinary skill in the art

to make the changes that would produce the patentee's" invention. *In re Chu*, 36 USPQ2d 1089, 1094 (Fed. Cir. 1995). In this case, the cited references **teach away** from the use of an aminosugar alone to treat synovitis, subchondral bone edema, and cartilage degradation. As such, the references do not reveal a reasonable expectation of success. *In re Dillon*, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990). Therefore, there is no suggestion or motivation to combine any or all of the references to arrive at the invention as claimed with a reasonable expectation of success. Additionally, the cited reference does not teach or suggest all of the recited claim limitations.

Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. §103 be withdrawn.

## CONCLUSION

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

Fees for a three month extension of time are submitted herewith. If any additional fees are due, the Commissioner is authorized to charge any fees, or make any credits, to Deposit Account No. 502235 referencing the above-identified attorney docket number.

Respectfully submitted,

Date: 3/24/10

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